REMARKS

Independent claims 22 and 30 have been amended to specify that the amount of the "at least one effervescent couple is between about 20% by weight and about 80% by weight." In each instance the amendments incorporate a prior dependent claim, specifically claims 23 and 36, respectively, which dependent claims have been canceled herein. Additional editorial amendments appear in claims 30 (element "a") and claim 32. No new matter is introduced in any of the amendments. No new search is required as the amendments involve only limitations found in dependent claims. Entry of the amendments and reconsideration of the claims are respectfully requested.

The Office Action mailed July 28, 2006 acknowledges that the Terminal Disclaimer previously filed has been reviewed and accepted and thereby obviates the prior provisional rejection of the pending claims under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 6,200,604 and claims 10-15 and claims 17-19 of U.S. 6,974,590.

Furthermore, the Office Action mailed July 28, 2006 maintains the provisional rejection of claims 22, 23, 25-27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 11/026,132; claims 1-30 of copending Application No. 11/027,353; claims 1-22 of copending Application No. 11/026,327; and claims 1-5, 7-10 and 12-17 of copending Application No. 10/977,029 (which application will become abandoned in favor of continuing application Serial No. 11/511,098 filed August 28, 2006, now pending). It is noted that if the claims of the present application are allowed in response to the present submissions, a terminal disclaimer over the pending claims of the cited

applications is not required. In any event, Applicants will submit an appropriate terminal disclaimer, if and when necessary to obviate these provisional rejections.

The Office maintains, "for the reasons of record," the rejection of claims 22, 23, 26, 27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 under 35 U.S.C. §103(a) as being unpatentable over *McCarty*, U.S. 5,073,374 (hereinafter "*McCarty*") in view of *Wehling et al.*, WO 91/04757 (hereinafter "*Wehling*") and further in view of *Streisand et al.* ("Buccal absorption of fentanyl is pH-dependent in dogs," Anesthesiology, (1995 Mar), 82 (3), pp. 759-64; hereinafter "*Streisand*"). This rejection is traversed.

Additionally, the Office maintains, "for reasons of record," the rejection of Claims 22, 23, 25-27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 under 35 U.S.C. §103(a) as being unpatentable over *Chen et al.* ("Studies on formulations of fentanyl buccal adhesive tablets," Zhongguo Yiyao Gongye Zazhi, 1997, 28 (3), 129-131 (hereinafter "*Chen*") in view of *Wehling* and further in view of *Streisand*. This rejection is traversed.

To briefly review, the invention is directed to a tablet comprising an active ingredient wherein the tablet composition effectively and significantly increases permeability of the active ingredient across the oral mucosa. The application teaches that this can be achieved by, for example, combining an active medicament with an effervescent couple and a pH adjusting substance, all of which are released into the oral cavity and permeate the oral mucosa. The pending claims, including the amendments previously entered to streamline prosecution, as well as the amendments included herein, are specifically directed to fentanyl or its pharmaceutically acceptable salt as the active ingredient, the amount of the effervescent couple is recited as between about 20% by weight and about 80% by weight of the

tablet composition and the pH adjusting substance is a basic material.

Starting on page 3 of the Action mailed July 28, 2006 the Office responds to the Declaration and arguments submitted by Applicants in the communication mailed April 19, 2006. The remarks hereinbelow address both the legal and factual issues identified in the Office's response. Applicants would appreciate any further issues that the Office may wish to identify in the event that the currently amended claims are not allowed and it becomes necessary to file an Appeal Brief.

Referring to the "reasons of record" (Office Action mailed October 19, 2005), it is learned that the claims have been rejected over *McCarty*, *Wehling* and *Streisand* on the following basis: *McCarty* teaches a fast dissolving buccal tablet for administration of active ingredients that exhibit poor bioavailability, including analgesics such as fentanyl. The Office acknowledges that *McCarty* doesn't disclose the use of an effervescent couple, but relies on *Wehling* for that element. It is said that *Wehling* discloses that analgesics are among the drugs that can be administered. Furthermore, the tablets of *Wehling* are said to dissolve in the mouth in between about 30 seconds and about 7 minutes and to mask the objectionable flavor of medicaments, facilitate tablet disintegration and provide pleasant organoleptic sensation. The Office concludes that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the fast dissolving buccal fentanyl tablets of *McCarty* in order to employ effervescent disintegration agents, the motivation being "to obtain even faster dissolution as well as masking the objectionable flavor or medicaments and providing pleasant organoleptic sensation as suggested by *Wehling*."

The Office further acknowledges that neither *McCarty* nor *Wehling* teach the use of a pH adjusting substance which is a base. That defect is said to be remedied by *Streisand*, which is said to teach that buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH becomes more basic, due to an increase in the fraction of unionized fentanyl. The Office concludes that it would have been obvious to modify the teachings of *Wehling* to employ an excess of carbonate source (base) used as the effervescent disintegration agent. The motivation for doing so is said to be to increase the availability of fentanyl and thus make the tablet more effective. This rejection is traversed.

As described, the Office begins its analysis by relying on *McCarty* for its disclosure of a fast dissolving buccal tablet as well as active ingredients including fentanyl. Significantly, *McCarty* relies on the use of a fast dissolving sugar excipient to achieve its fast dissolving tablet, even though other disintegrants, both effervescent and noneffervescent, were known at the time. *McCarty* discloses that its formulations "upon administration disintegrate in about 30 seconds to about 5 minutes and preferably in about one minute." (Id., col. 2, lns. 51-53) As discussed above, the Office looks to *Wehling* in order to displace the fast dissolving sugar of *McCarty* with an effervescent disintegration agent, the alleged motivation for doing so said to be "to obtain even faster dissolution" as well as other ostensible benefits. However, the Office acknowledges that "the tablets of *Wehling* dissolve in the mouth in between about 30 seconds and about 7 minutes." (*Id.*, page 8, lns. 1-2) Therefore, absent Applicants' teaching of a more significant benefit for the use of an effervescent couple, one skilled in the art faced with the problem of improving delivery of a drug with poor bioavailability would not reasonably look to *Wehling*

to obtain equivalent rates. In fact, *Wehling* discloses that a particularly preferred embodiment dissolves in the mouth in "between about 30 seconds and about 5 minutes" (page 13, lns. 21-24) whereas the preferred dissolution rate of *McCarty* is "about one minute." (col. 2, ln. 53)

Furthermore, there is no evidence of record that fentanyl or its salts, the sole active ingredient currently claimed, has a taste that requires "masking" which is said to be another possible benefit of *Wehling*. But, weighing against any need for masking is the fact that fentanyl is currently administered to patients in the form of a "lollypop" under the brand name "Actiq." The literature for "Actiq" does not suggest a coated active or use of effervescence for taste masking. Furthermore, in this form fentanyl is directly administered in the mouth over an extended period of time. Finally, there is no suggestion that the organoleptic sensation of an effervescent disintegrant offers any motivation compared to the fast dissolving sugar employed by *McCarty*. In short, the alleged motivation to modify *McCarty* by disregarding its fast dissolving sugar and substituting the effervescent disintegrant of *Wehling* can be seen as an exercise for disclosure of the present invention in order to identify one element of its unique multicomponent composition that has been shown to surprisingly and significantly increase permeability of fentanyl across the oral mucosa.

Furthermore, it is important to note that the pH proposed in *Streisand* is insufficient to achieve a significant benefit in the oral transmucosal permeability of fentanyl, as clearly demonstrated by the data introduced by Applicants in the Declaration previously submitted, and there is nothing in the art relied on by the Office to suggest a significant improvement in oral transmucosal permeability of fentanyl by combining a pH

adjustment with *any* other element or variable. In particular, the pH effect in *Streisand* was achieved using fentanyl solutions in extended contact (60 min.) over a large surface area (18 cm^2) using a cell clamped to the buccal mucosa of a dog. In contrast, there is nothing in *Streisand* to suggest that a practical effect can be achieved using a composition that is typically in the form of a dispersion and is in transient contact *in vivo* for a limited time period and in a limited amount of saliva. According to its own disclosure, *Streisand* is not a teaching of how to effect an improvement in "real time" or under practical conditions, as achieved by the present invention. For example, the *Streisand* authors question the practical significance of their own experiments, "Can the results of our study be related to clinical practice? The variability in fentanyl absorption from oral transmucosal fentanyl citrate (OTFC) may result, in part from variations in mouth pH." (page 5, last column) In other words, while the paper represents a general confirmation of the Henderson-Hasselbach effect disclosed by Applicants starting at page 5, line 27, there is little to suggest that a pH change can have a practical effect.

Significantly, even though the *Streisand* objective was to increase permeability of fentanyl across the oral mucosa, the authors failed to appreciate that the use of an effervescent couple in combination with an increase in pH could achieve such a result in "clinical practice." At best, this reference is an invitation to experiment, a suggestion that adjusting the pH might lead to some benefit. However, in order to achieve the significant improvement demonstrated by Applicants, it would be necessary to test a combination of a change in pH with essentially all available excipients that are typically used in pharmaceutical formulations, in order to determine if a

meaningful improvement in transmucosal permeability could be achieved. This merely injects an improper "obvious to try" consideration and a number of decisions reject "obvious to try" as a test of obviousness under Section 103. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988) ("whether a particular combination might be 'obvious to try' is not a legitimate test of patentability"); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 USPQ2d 1923, 1928 (Fed. Cir. 1990) ("we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 USC 103.") In a typical "obvious to try" situation, the inventor selects a particular feature from a range of possibilities suggested by the prior art and discovers that the claimed feature achieves significant advantages nowhere suggested in the prior art. In such cases, it is clear that the result achieved must be considered as well as the actual physical modification. In other words, one must consider the "differences between the prior art and the claims at issue," *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459 (1966), (including the result or effect achieved). The result also is part of the "subject matter as a whole," which also must be obvious under Section 103 for the claims to be deemed obvious. In the present circumstances, Applicants have clearly provided evidence that significant advantages are achieved and the magnitude of such advantages are nowhere to be found or suggested in the art relied on to reject the claims.

In dismissing the significance of the data introduced by Applicants in the Declaration submitted in the prior response, the Office begins with its conclusion, "the increased fentanyl permeability due to the presence of both an effervescent couple and a pH adjusting agent (i.e., base) as demonstrated in the declaration is not unexpected." (*Id.*, page 4) The Office cites *Streisand* for support of the pH effect and refers to *Wehling* as

teaching the following alleged benefits for using "effervescent disintegration agents": "masking the objectionable flavor of medicaments, facilitating disintegration of the tablet and providing pleasant organoleptic sensation." (*Id.*)

At least two issues are significant in this analysis by the Office. First, the claims require an "effervescent couple present in an amount which is greater than the amount necessary for tablet disintegration, wherein said amount of said at least one effervescent couple is between about 20% by weight and about 80% by weight." (Claim 1, emphasis added) In contrast, the art relied on by the Office, as well as the conclusion quoted above, merely requires an amount that is sufficient to function, e.g., as a disintegration agent or to provide a pleasing organoleptic effect, etc. There is no suggestion or motivation to increase the amount to a level which, in combination with an increase in pH, would result in significantly increased transmucosal permeability of fentanyl, particularly since such an effect was wholly unrecognized in the cited art.

Second, the Office concludes as it begins, "Therefore, one skilled in the art would have expected an increased absorption, bioavailability and permeability of fentanyl through the oral mucosa following an increase in pH." (*Id.*) If the dismissal of the evidence submitted by Applicants is to be based on the art relied on then it should refer to more than just 'an increase' "following an increase in pH." The claims include both an effervescent couple at an effective level and a basic pH adjusting substance. There is nothing in the art relied on by the Patent Office to suggest that fentanyl permeability across the oral mucosa from a composition containing both an effervescent couple and pH adjusting substance would be more than 510% greater than a composition containing only a pH adjusting substance and more than 410% greater than that for the

composition containing only an effervescent couple. In other words, even a moderate improvement that might be observed with the use of a pH adjusting substance alone, while consistent with Applicants' own disclosure relating to the Henderson-Hasselbach equation and with *Streisand*, is overwhelmed by the combined effect of an effervescent couple and a pH adjusting substance. And there is absolutely nothing in the art relied on to lead one skilled in the art to expect that when a pH adjusting substance is combined with another, quite ordinary, well-known pharmaceutical excipient, an effervescent agent, a significant improvement in fentanyl permeability will be obtained.

Importantly, there is nothing in the art relied on, *McCarty*, *Wehling*, *Streisand* or *Chen*, to suggest that the use of an effervescent couple would have a significant effect on oral transmucosal permeability of fentanyl. Indeed, the art does not even allow one to expect an additive effect. In contrast, Applicants previously submitted a Declaration that clearly demonstrates an improvement in permeability that far exceeds the additive. Such an improvement could not have been expected by a skilled person in the art even if they had been motivated to make the compositional changes suggested by the Office. "One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Dir. 1995)

Finally, one additional comment is necessary in view of the Office's "Response to Declaration and Arguments" in paragraphs 9-11 of the Office Action. In rejecting Applicants' arguments concerning *Wehling*, the Office states, "Contrary to Applicant's assertion, *Wehling et al.* does not require that the active

ingredient be present as "coated microparticles," it is merely one of the embodiments of the *Wehling's* invention. See *Wehling et al.* @ p. 6, lines 27-38." The difference between Applicants' view and the Office's view regarding the teaching of *Wehling* is significant since it bears on whether or not *Wehling* teaches or suggests that an active ingredient is transferred across the oral mucosa, and especially whether or not it is an appropriate reference for combination with *McCarty* and/or *Streisand* or *Chen*, etc. The portion of *Wehling* relied on by the Office reads as follows:

> "According to a further aspect of the present invention, the systemically distributable pharmaceutical ingredient is preferably a pharmaceutical ingredient which may be provided in microencapsulated form. Thus, the mixture may include microcapsules each incorporating a systemically distributable pharmaceutical ingredient and an encapsulant surrounding the pharmaceutical ingredient. Upon disintegration of such a tablet, the individual microcapsules are released and dispersed in the patient's mouth in admixture with the patient's saliva whereupon the microcapsules are conducted to the digestive tract for systemic distribution." (Emphasis added)

It appears that the Office is relying on the underlined language to suggest that *Wehling* provides a broader teaching than an encapsulated active ingredient which passes into the digestive tract after the tablet disintegrates in the mouth due to the presence of an effervescent disintegrant.

However, considering the whole of the *Wehling* disclosure, the Office is taking the quoted portion significantly out of context in order to reach the effervescent couple elements of Applicants' claims. It is clear that *Wehling* discloses

compositions in which the active is isolated from the oral mucosa, except in those accidental circumstances where a coated particle of the active is damaged and the active is exposed (thereby also obtaining the benefit of an effervescent disintegrant in its function as a taste masking element; see page 18, ln. 29 to page 19, ln. 10). It is particularly noteworthy that *Wehling* et al. characterize their invention as follows:

> "The combination of the effervescent disintegration agent and the microcapsules provides a uniquely effective dosage form for systemically distributable pharmaceutical ingredients which have unpleasant flavors or which should not be released within the mouth for other reasons." (Page 7, lns. 1-6; emphasis added.)
>
> "Also provided hereby is a method of administering a microencapsulated systemically distributable pharmaceutical ingredient to a patient. This is accomplished by placing a tablet as discussed above which includes at least one microencapsulated systemically distributable pharmaceutical ingredient into the mouth of a patient whereupon the tablet completely dissolves without chewing or crushing by mastication. The intact microcapsules released into the saliva thereby are conducted to the digestive tract for systemic distribution of the pharmaceutical ingredient encapsulated therein." (Page 7, ln. 31-page 8, ln. 4; emphasis added.)
>
> "By the use of the present invention, the microencapsulated systemically distributable pharmaceutical ingredient is delivered to the digestive

system as a suspension or slurry of microcapsules." (Page 19, lns. 14-18)

From the whole of the disclosure of *Wehling*, it is apparent that its invention and its teachings are not relevant to compositions or methods for the delivery of an active ingredient across the oral mucosa. Furthermore, the effervescent couple of *Wehling* serves primarily as a disintegrant and organoleptic aid, as also acknowledged by the Office, and there is no suggestion that any amount should be used in excess of that required for its disclosed purposes, such as an amount necessary to increase permeability across the oral mucosa. ("The effervescent disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide a distinct sensation of effervescence when the tablet is placed in the mouth of a patient." Page 4, lns. 4-8) Applicants again emphasize that *McCarty* is directed to delivery of an active in the mouth whereas *Wehling* is directed to delivery through the digestive system. The disclosure of *Wehling* regarding the use of a protective coating is substantial whereas there is no corresponding, meaningful teaching relating to intentional delivery of an active via the oral mucosa.

Applicants reaffirm the arguments in the prior amendment traversing rejection of the claims under 35 U.S.C. §103(a) in view of *Chen* in view of *Wehling* and further in view of *Streisand*.

In conclusion, Applicants have demonstrated that the combination of claimed ingredients results in a significant and surprising effect that could not have been expected based on the art relied on by the Office. Furthermore, the demonstrated level of improvement based on the claimed elements is such as to outweigh even a *prima facie* obviousness rejection, assuming for

the sake of argument that the combination of selective features taken from the cited references, *McCarty, Wehling, Streisand* and *Chen*, are accepted at face value and applied as suggested by the Office. Finally, it is respectfully suggested that in view of the inapplicability of *Wehling* as a reference that can or should be relied on to reject the claims under 35 U.S.C. §103(a), as discussed above, a *prima facie* obviousness rejection has not be made. Withdrawal of the rejections is respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections that she might have.

If there are any additional charges in connection with this requested amendment, the examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: October 27, 2006

Respectfully submitted,

By _____

Harvey L. Cohen
Registration No.: 28,365
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000
Attorney for Applicants

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